OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
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Peer Review Report for "Comparison of Postoperative Prognosis Among HBV-Related, HCV-Related, and non-HBV non-HCV Hepatocellular Carcinomas: A Systematic Review and Meta-analysis"

Author(s): Yue Zhao, Yuanyuan Jia, Sufen Qi, Chensi Wu, Jianhua Wu, Ruixing Zhang, Jing Li, Zhanjun Guo

Review Timeline:

Submit Date:	17 Dec 2021
Revised Date:	22 Jun 2022
Accepted Date:	23 Jun 2022

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

9 Jan 2022

The current manuscript is a well-written meta-analysis comparing HCC clinical features and prognosis among three subgroups of patients based on their HBV/HCV status. The study investigates tumor characteristics and liver function tests, as well as 5-year overall and recurrence-free survival. Despite the availability of some recent studies relevant to the investigated subject, the most recent study used in this meta-analysis dates back to 2017. Also, the majority of these investigated studies have been conducted in Asian countries. However, considering the inconsistency between studies on viral hepatitis-related HCC characteristics, and the growing number of such studies in the last decades, I believe the current systematic review provides a comprehensive review in the field and is suitable for publication after minor revisions.

Here are some comments for the authors:

Context:

1st paragraph: The introduction starts with two sentences that contain many numbers. I suggest choosing a more straightforward sentence for the beginning.

2nd paragraph: In the following sentence, please clarify “other patients”:
“According to Li et al. (8) study with 413 patients, the HCV-HCC displayed a lower 5-year survival rate accompanied with a higher intrahepatic and multiple recurrence rates than those of the other patients”

Conclusions:

1st paragraph: I would modify the first paragraph of the conclusions to improve coherency. The general fellow of the paragraph seems reasonable but can be described in a way that makes more sense to the reader.

2nd paragraph: Please rephrase the following sentence:
“Androgen receptor enhances hepatic telomerase reverse transcriptase gene (TERT) transcription through HBV integration or point mutation at promoter region was discovered as a mechanism for the male dominance of HBV-HCC”

2nd paragraph: In general, the proportion of males is usually higher among HCV patients compared to HBV patients, due to the higher prevalence of risky behaviors. In this study, the male proportion was lower in the HCV-HCC group compared to HBV-HCC and NBNC-HCC groups. Authors may have an explanation for this finding and can compare their results with similar studies.

3rd paragraph: Consider revising the following sentence:
The fact that HCV-HCC group had lowest liver reserve function and highest ratio of cirrhosis in the three groups, which might be explained by the directed damage to hepatocytes initiated by HCV infection through increasing the permeability of lysosomal membrane and expression of toxic proteins.

6th paragraph: I believe authors should expand on the differences in 5-year overall and recurrence-free survival of their three investigated groups. Comparisons with similar meta-analyses and systematic reviews or other population-based studies may be interesting, since this is one of the main focuses of the present study.

References:

There are several recent valuable studies that could have been considered by the authors:

E Tabrizian et al. Outcomes of transplantation for HBV- vs. HCV-related HCC: impact of DAA HCV therapy in a national analysis of >20,000 patients. HPB (Oxford). 2021 Dec

De Battista D et al. Molecular Signature and Immune Landscape of HCV-Associated Hepatocellular Carcinoma (HCC): Differences and Similarities with HBV-HCC.

Akkiz H et al. Plasma lipids, tumor parameters and survival in HCC patients with HBV and HCV.

Tables:

Table 2: I suggest modifying this table to improve readability. It is difficult to distinguish the subgroups of the first column in the current format.

REFEREE: Reviewer | **Revision** (0) 1 Feb 2022

Based on the Cochrane principle, the systematic review and meta-analysis studies should be searched four databases which included PubMed (Medline), Scopus, Embase, and Web of Sciences. In this meta-analysis, these databases were not searched completely. Also, the search strategy and search syntax are not clear.
Have you registered the protocol for this review?
It is necessary that the authors explained how to calculate HR in case-control studies.
Are you sure that the combined case-control and cohort studies and finally report pooled HR is true? I think that extracted HR in the two studies are very different.
The statistical analysis needs to report related references.
In the results section, it is necessary that the author reports between-group statistically significant.
I think that the authors better used the fixed-effect model. Because the calculated weights in the forest plots same together.
It is better that the subgroup analysis is performed based on the type of studies (case-control or cohort studies). one challenge that is really important, do you authors are sure the case-control studies are suitable for calculated and reported survival rate?

REFEREE: Associate Editor | **Revision** (0) 25 Mar 2022

Dear EIC,

The manuscript was reviewed by 2 experts. The study results are interesting, however, there are major concerns raised by the reviewers, especially with data analysis and

presentation. I have more to add:

1. The English writing and academic presentation of manuscript should be improved with the help of a colleague who is expert in academic writing or using the commercial services.

2. I guess, the studies have been selected initially based on availability of survival analysis. Pooling data of characteristics was performed in the above-mentioned studies. Since there is a bias on initial selection of studies and missing HCC studies without evaluation of survival, it cannot be a meta-analysis of HCC characteristics by the HCC underlying disease. I recommend authors to take These into the manuscript.

3. In Exclusion criteria, "those with small sample size or large amount of censored data." What is the definition of small sample size and large amount of censored data in this study?

4. The presentation of P-values should be uniform. Currently, there is no uniform rule for the presentation of P-values such as P=0.000, P<0.05 and P<0.01

5. The term "risk factor" is vague in title of Table 2. I suggest the term "characteristics" as used by the authors as well.

6. I have major concern with pooling the characteristics as it is currently done by the authors. How did the authors select the studies for inclusion in pooling for characteristics? HR is an index of survival. How can it be used for comparison of characteristics? How the pooling was performed for the characteristics data?

7. I have major concern with presentation of HR results for survival data. HR is obtained from calculation of mortality or recurrence in a group comparing another group. knowing which group is the reference is important in presentation of figures, tables and result body. For example, "the 5-year overall survival rates were lower in HBV-HCC (HR:0.86, 95% CI: 0.78 to 0.95, P=0.002) and HCV-HCC group (HR:0.87, 95% CI: 0.80 to 0.94, P=0.000) than that in NBNC-HCC group." The reference group based on the sentence structure and Figure 2 is NBNC-HCC group. The HR less than 1 is in favor of higher survival. Here the HRs are less than 1 and it has been stated that the survival is lower in HCV and HBV groups than NBNC group. This issue should be deeply considered in writing and presentation of results.

8. Where are the "Sensitivity analysis" results?

Regards,
AE

Seyed Moayed Alavian: EIC | **Revision** (**0**) 25 Mar 2022

Dear Authors,

Thank you for the submission. Please follow the peer-review comments and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Detailed Responses to the Reviewers and Associate Editor

We sincerely thank the reviewers and associate editor for the constructive comments, which have greatly optimized our manuscript.

According to these kind suggestions, we have systematically and comprehensively searched multiple electronic databases to supplement all available articles. Our manuscript and the supplementary materials have been carefully revised according to the reviewer's instructions. In the following, we respond to the comments one by one, with every comment listed first and the corresponding response following.

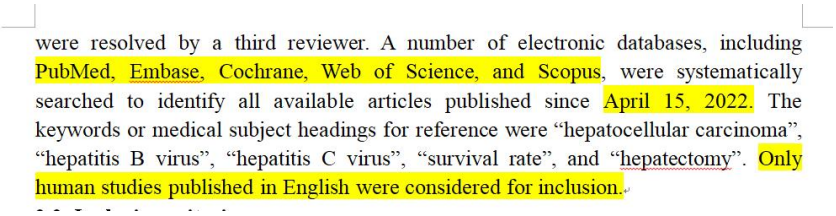
Response to Reviewer 1

Comment 1:

Based on the Cochrane principle, the systematic review and meta-analysis studies should be searched four databases which included PubMed (Medline), Scopus, Embase, and Web of Sciences. In this meta-analysis, these databases were not searched completely. Also, the search strategy and search syntax are not clear.

Response 1:

We would like to sincerely thank the reviewer for carefully assessing our manuscript and raising the constructive comment. Extensive and comprehensive literature collection is very necessary for the implementation of the systematic review and meta-analysis studies. Therefore, we systematically and comprehensively searched multiple electronic databases, including PubMed (Medline), Embase, Cochrane, Web of Science, and Scopus, to supplement all available articles. The number of relevant studies from the preliminary systematic search increased from 260 to 733. Finally, 26 studies, involving 20381 participants were identified as eligible papers that had been published between 1997 and 2021. Two new literatures have been added to this systematic review and meta-analysis. Meanwhile, the search strategy and search syntax were improved and supplemented at the end of the first paragraph in part 2.1. Some of the modifications are shown below (marked as yellow).



were resolved by a third reviewer. A number of electronic databases, including PubMed, Embase, Cochrane, Web of Science, and Scopus, were systematically searched to identify all available articles published since April 15, 2022. The keywords or medical subject headings for reference were "hepatocellular carcinoma", "hepatitis B virus", "hepatitis C virus", "survival rate", and "hepatectomy". Only human studies published in English were considered for inclusion.

Comment 2:

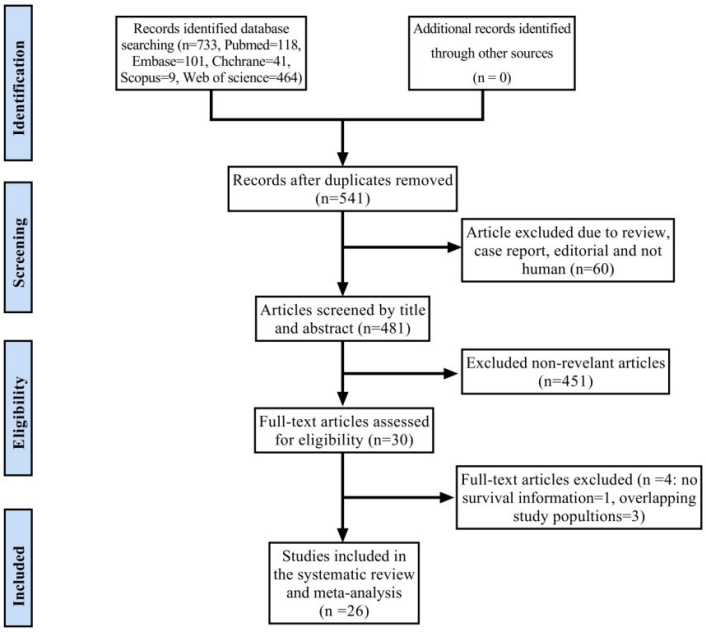
Have you registered the protocol for this review?

Response 2:

We thank the reviewer for raising this important comment. Unfortunately, this review has not been registered, but it was carried out in strict accordance with the process of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

In this review, we try our best to minimize bias and produce reliable findings to provide basis

for the treatment of HCC patients. Firstly, screening and data extraction were completed by two independent reviewers, and differences were resolved by a third reviewer. Secondly, publication bias was assessed using *Begg's test* and *Egger's test*. Nevertheless, we also wrote a limitation in the limitation section: this review was not registered, but this meta-analysis was carried out in strict accordance with the PRISMA statement. The following figure is the flow diagram of the selection process of the included studies in this systematic review.



Comment 3:

It is necessary that the authors explained how to calculate HR in case-control studies.

Response 3:

Thank you very much for the constructive suggestions. A total of 26 studies were included in this review. By carefully rereading these articles, we found that all articles were retrospective cohort studies rather than case-control studies. Therefore, the observation indexes we extracted were consistent.

Comment 4:

Are you sure that the combined case-control and cohort studies and finally report pooled HR is true? I think that extracted HR in the two studies are very different.

Response 4:

Thank you very much for your professional suggestions. As mentioned above, all studies included in this review were retrospective cohort studies, and the HR was genuine and believable. In addition, the inclusion criteria were also modified, and the study design type was set as the cohort study.

Comment 5:

The statistical analysis needs to report related references.

Response 5:

Thanks for the important suggestions. We have added references of statistical analysis.

11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700.
12. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010 Sep; 25(9):603-5.
13. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun;21(11):1539-58.

Comment 6:

In the results section, it is necessary that the author reports between-group statistically significant.

Response 6:

Thanks for the important suggestions. To further assess the heterogeneity of clinical significance, subgroup analyses were performed according to mean tumor size, serum alpha-fetoprotein level, serum ALB level and country. For those with differences between groups, the results of two-way comparison were P>0.05, indicating that they were balanced and comparable. Similarly, no statistically significant differences were demonstrated among these subgroups. We have added relevant data in Table 3-5.

Comment 7:

I think that the authors better used the fixed-effect model. Because the calculated weights in the forest plots same together.

Response 7:

Thank you very much for your professional suggestions. According to relevant standards in the Cochrane Intervention System Evaluation Manual, the fixed-effect method was used if heterogeneity was acceptable (I^2<50%, P>0.10),the random-effect method was used if heterogeneity was established (I^2≥50%, P < 0.10). Because of the clinical heterogeneity inherent in the data, we used random-effects model for all meta-analyses. In addition, one of included articles is a large sample size study with 11950 cases (Utsunomiya et al. [14]), whose large weight value might affect the balance of the results. By using the random-effect model, the weight of small sample research was given priority to make the results more credible.

Comment 8:

It is better that the subgroup analysis is performed based on the type of studies (case-control or cohort studies). one challenge that is really important, do you authors are sure the case-control studies are suitable for calculated and reported survival rate?

Response 8:

We thank the reviewer for raining this constructive comment. In this review, all articles were retrospective cohort studies. Therefore, we did not conduct subgroup analysis according to the type of studies.

Response to Reviewer 2:

We sincerely thank the reviewers for the constructive comments, which have greatly optimized our manuscript. Our manuscript and the supplementary materials have been carefully revised according to the reviewer's instructions. In the following, we respond to the comments one by one, with every comment listed first and the corresponding response following.

Comment 1:

Context:

1st paragraph: The introduction starts with two sentences that contain many numbers. I suggest choosing a more straightforward sentence for the beginning.

Response 1:

We thank the reviewer for this kind reminder. We have made corresponding modifications (the modified part has been marked in yellow).

Comment 2:

2nd paragraph: In the following sentence, please clarify “other patients”:

“According to Li et al. (8) study with 413 patients, the HCV-HCC displayed a lower 5-year survival rate accompanied with a higher intrahepatic and multiple recurrence rates than those of the other patients”

Response 2:

We sincerely thank the reviewer for carefully reviewing our manuscript. We have revised this sentence to replace "other patients" with "hepatitis B virus related hepatocellular carcinoma (HBV-HCC) and non-HBV non-HCV hepatocellular carcinoma (NBNC-HCC) ". The modified part has been marked yellow.

Comment 3:

Conclusions:

1st paragraph: I would modify the first paragraph of the conclusions to improve coherency. The general fellow of the paragraph seems reasonable but can be described in a way that makes more sense to the reader.

Response 3:

Thank you very much for the constructive suggestions. The suggestion was well taken. We have made comprehensive revisions to the first paragraph of the conclusion to improve the logicality. The modification details are as follows.

HBV and HCV are both hepatotropic viral infections with significantly different molecular carcinogenic mechanisms. The carcinogenic potential of HBV is due to its ability to integrate into the DNA of host cells, directly activate adjacent cellular genes, and provide selective growth advantages for hepatocytes (42). In contrast, HCV is a positive-strand RNA virus that cannot integrate into the genome of liver cells; therefore, it likely promotes hepatocarcinogenesis through chronic inflammation, liver regeneration, and fibrosis rather than direct carcinogenesis (43). Additionally, the carcinogenic mechanism of NBNC-HCC is significantly different from that of virus-related HCC. The exact molecular mechanism for the increase in NBNC-HCC incidence rate is still indistinct, possibly caused in part by the changing prevalence of non-alcoholic steatohepatitis and metabolic syndrome (1). The difference in etiology and pathogenesis of HCC might lead to unique clinicopathological characteristics and prognosis in patients with HCC. The present study examined the differences in clinical characteristics and postoperative prognosis of HCC with different viral statuses and found that the prognosis of patients with NBNC-HCC was superior to that of patients with HBV-HCC and HCV-HCC in terms of OS and RFS. Meanwhile, patients with HBV-HCC had a longer RFS than patients with HCV-HCC. Furthermore, our research found that HBV-HCC, HCV-HCC, and NBNC-HCC differed significantly in the aspects of clinical features, liver function, and tumor characteristics.

Comment 4:

2nd paragraph: Please rephrase the following sentence:

"Androgen receptor enhances hepatic telomerase reverse transcriptase gene (TERT) transcription through HBV integration or point mutation at promoter region was discovered as a mechanism for the male dominance of HBV-HCC"

Response 4:

Thanks for the important suggestions. We have made the following modification to this sentence:

"Androgens directly interact with the HBV genome integrated into the cell nucleus and activate the transcription of HBV oncoproteins."

Comment 5:

2nd paragraph: In general, the proportion of males is usually higher among HCV patients compared to HBV patients, due to the higher prevalence of risky behaviors. In this study, the male proportion was lower in the HCV-HCC group compared to HBV-HCC and NBNC-HCC groups. Authors may have an explanation for this finding and can compare their results with similar studies.

Response 5：

Thank you very much for your kind advice. Our data showed that the proportion of male patients was lower in HCV-HCC group than that in HBV-HCC and NBNC-HCC groups. At present, the mechanism of gender difference in hepatitis virus related HCC is still unknown. However, previous similar studies have yielded results consistent with ours.

[1] T Ishikawa, T Ichida, S Yamagiwa, et al. High viral loads, serum alanine aminotransferase and gender are predictive factors for the development of hepatocellular carcinoma from viral compensated liver cirrhosis. J Gastroenterol Hepatol. 2001;16(11):1274-81.

[2] Omichi K, Shindoh J, Yamamoto S, et al. Postoperative Outcomes for Patients with Non-B Non-C Hepatocellular Carcinoma: A Subgroup Analysis of Patients with a History of Hepatitis B Infection. Ann Surg Oncol. 2015;22 Suppl 3:S1034-40.

Comment 6:

3rd paragraph: Consider revising the following sentence:

The fact that HCV-HCC group had lowest liver reserve function and highest ratio of cirrhosis in the three groups, which might be explained by the directed damage to hepatocytes initiated by HCV infection through increasing the permeability of lysosomal membrane and expression of toxic proteins.

Response 6： Thanks for the important suggestions. We have made the following modifications to this sentence.

The fact that the HCV-HCC group had the lowest liver reserve function and the highest ratio of cirrhosis among the three groups was similar to the conclusions of previous studies (10,14). ~~may be explained by the direct damage to hepatocytes initiated by HCV infection by increasing the permeability of the lysosomal membrane and the expression of toxic proteins.~~ The complex interaction between HCV and host proteins has the potential to cause host responses, increase inflammation and fibrosis, and finally lead to liver cirrhosis (55).

Comment 7:

6th paragraph: I believe authors should expand on the differences in 5-year overall and recurrence-free survival of their three investigated groups. Comparisons with similar meta-analyses and systematic reviews or other population-based studies may be interesting, since this is one of the main focuses of the present study.

Response 7:

We thank the reviewers for this important comment. As you have mentioned， the main focuses of this study are the differences in the 5-year overall survival rate and recurrence-free survival rate of HCC in different hepatitis states. Therefore, we moved the sixth paragraph to the second paragraph, and compared our results with similar meta-analyses and large sample size single-center studies. The details are as follows.

Previous studies have compared the prognostic differences between virus-related HCC and NBNC-HCC, with inconsistent results (10,14,44). A retrospective single-center study reported that the presence of viral hepatitis did not significantly affect long-term prognosis after surgical treatment in patients with HCC (44). A meta-analysis of 4744 patients showed that patients with NBNC-HCC had better 5-year DFS and a tendency toward higher 5-year OS (not statistically significant) than HCC patients with HBV or HCV infection. However, there was no difference in survival between the HBV-HCC and HCV-HCC groups (10). In another large-sample study of 11950 cases, the result showed that the NBNC-HCC group had a significantly lower risk of recurrence than the HBV-HCC and HCV-HCC groups (14). Similarly, our data from 20381 patients confirmed that patients with NBNC-HCC had better 5-year OS and RFS than those with HBV-HCC or HCV-HCC. Cancer-promoting factors in the inflammatory microenvironment of hepatitis result in gene mutation and chromosomal instability in hepatocytes, leading to intrahepatic recurrence, which is the main cause of death in patients with HCC postoperatively (45,46). Therefore, we believe that the improved survival rate of NBNC-HCC is because of the absence of chronic viral attack, and that patients with NBNC-HCC maintained good liver function following the initial hepatectomy. These biological advantages provide more opportunities for antitumor treatment (34). In addition, we found that the 5-year RFS rate of patients with HCV-HCC was lower than that of patients with HBV-HCC. Franssen et al. (47) found that the postoperative recurrence rate of HBV-HCC was lower than that of HCV-HCC. Previous studies have demonstrated that HCC with different viral etiologies has unique molecular signatures and immune landscapes. Compared with HBV-HCC, HCV-HCC leads to downregulation of T-cell-related genes within the tumor and upregulation of oxidative stress genes outside the tumor, and the persistent necrotic inflammatory environment might cause recurrence (48). Therefore, effective therapy could prevent postoperative recurrence and improve OS of patients with virus-related HCC through viral inhibition and anti-inflammatory effects (49). A large prospective study published in 2021 indicated that direct-acting antiviral (DAA) medication enhanced survival of patients with HCV-HCC after liver transplantation and was comparable to patients with HBV-HCC (50).

Comment 8:

References:

There are several recent valuable studies that could have been considered by the authors:

E Tabrizian et al. Outcomes of transplantation for HBV- vs. HCV-related HCC: impact of DAA CV therapy in a national analysis of >20,000 patients. HPB (Oxford). 2021 Dec

De Battista D et al. Molecular Signature and Immune Landscape of HCV-Associated Hepatocellular Carcinoma (HCC): Differences and Similarities with HBV-HCC.

Akkiz H et al. Plasma lipids, tumor parameters and survival in HCC patients with HBV and HCV.

Response 8:

We thank the reviewer for this constructive suggestion and the kind reminder. We found the

abovementioned references very interesting and helpful. Therefore, we have added the following representative references.

and immune landscapes. Compared with HBV-HCC, HCV-HCC leads to downregulation of T-cell-related genes within the tumor and upregulation of oxidative stress genes outside the tumor, and the persistent necrotic inflammatory environment might cause recurrence (48). Therefore, effective therapy could prevent postoperative recurrence and improve OS of patients with virus-related HCC through viral inhibition and anti-inflammatory effects (49). A large prospective study published in 2021 indicated that direct-acting antiviral (DAA) medication enhanced survival of patients with HCV-HCC after liver transplantation and was comparable to patients with HBV-HCC (50).

48. De Battista D, Zamboni F, Gerstein H, Sato S, Markowitz TE, Lack J, et al. Molecular Signature and Immune Landscape of HCV-Associated Hepatocellular Carcinoma (HCC): Differences and Similarities with HBV-HCC. J Hepatocell Carcinoma 2021 Nov;8:1399-1413.

49. Miao RY, Zhao HT, Yang HY, Mao YL, Lu X, Zhao Y, et al. Postoperative adjuvant antiviral therapy for hepatitis B/C virus-related hepatocellular carcinoma: a meta-analysis. World J Gastroenterol. 2010 Jun 21;16(23):2931-42.

50. Tabrizian P, Saberi B, Holzner ML, Rocha C, Kyung Jung Y, Myers B, et al. Outcomes of transplantation for HBV- vs. HCV-related HCC: impact of DAA HCV therapy in a national analysis of >20,000 patients. HPB (Oxford). 2021 Dec;S1365-182X(21)01723-8.

Comment 9:

Tables:

Table 2: I suggest modifying this table to improve readability. It is difficult to distinguish the subgroups of the first column in the current format.

Response 9:

Thank you for the reminder. The suggestion was taken fully. Readability of table is truly very important. We made the following modifications.

Table 2 Meta-analysis of characteristics for HCC patients with different hepatitis virus status

Characteristic	Group	Number of studies	Number of patients	Results	RR/WMD	95% CI	*P*-value	I^2 (%)
Age (years)	HBV-HCC vs. HCV-HCC	14 [8, 9, 15-17, 19-21, 24, 25, 30, 32, 33, 36]	4714	HBV-HCC=55.8±11.7 HCV-HCC=67.3±7.9	-10.06	-11.51, -8.62	0.000	74.8
	NBNC-HCC vs. HBV-HCC	11 [8, 9, 15, 16, 19, 20, 24, 25, 30, 32, 33]	1777	HBV-HCC=55.8±10.4 NBNC-HCC=68.2±9.3	-10.52	-12.83, -8.22	0.000	82.3
	NBNC-HCC vs. HCV-HCC	11 [8, 9, 15, 16, 19, 20, 24, 25, 30, 32, 33]	3575	HCV-HCC=67.6±7.8 NBNC-HCC=68.0±9.6	-0.34	-1.65, 0.97	0.612	70.1
Gender	HBV-HCC vs. HCV-HCC	22 [8, 9, 14-17, 20-28, 30-34, 36, 37]	15839	HBV-HCC=81.6% HCV-HCC=73.4%	1.09	1.05, 1.13	0.000	51.4
	NBNC-HCC vs. HBV-HCC	16 [8, 9, 14-16, 20, 24-26, 30-35, 37]	7909	HBV-HCC=82.6% NBNC-HCC=81.8%	1.02	0.98, 1.07	0.297	38.6
	NBNC-HCC vs. HCV-HCC	15 [8, 9, 14-16, 20, 24-26, 30-34, 37]	14238	HCV-HCC=73.5% NBNC-HCC=81.8%	0.90	0.89, 0.92	0.000	0
Serum ALT level (IU/L)	HBV-HCC vs. HCV-HCC	13 [8, 9, 16, 17, 19, 20, 23, 25, 27, 30, 32, 33, 36]	3663	HBV-HCC=48.6±41.9 HCV-HCC=60.3±43.6	-16.97	-21.70, -12.24	0.000	45.1
	NBNC-HCC vs. HBV-HCC	9 [8, 9, 16, 19, 20, 25, 30, 32, 33]	1564	HBV-HCC=48.1±40.4 NBNC-HCC=42.5±34.2	4.13	0.74, 7.52	0.017	0
	NBNC-HCC vs. HCV-HCC	9 [8, 9, 16, 19, 20, 25, 30, 32, 33]	3253	HCV-HCC=58.9±42.4 NBNC-HCC=42.6±34.0	21.02	13.19, 28.85	0.000	85.4
Serum AST level (IU/L)	HBV-HCC vs. HCV-HCC	10 [9, 16, 17, 19, 23, 25, 30, 32,33, 36]	2856	HBV-HCC=48.7±44.5 HCV-HCC=60.9±39.8	-14.19	-17.17, -11.22	0.000	29.5
	NBNC-HCC vs. HBV-HCC	7 [9, 16, 19, 25, 30, 32, 33]	1114	HBV-HCC=46.7±43.0 NBNC-HCC=42.6±37.5	0.51	-4.75, 5.78	0.848	43.2
	NBNC-HCC vs. HCV-HCC	7 [9, 16, 19, 25, 30, 32, 33]	2713	HCV-HCC=59.5±38.8 NBNC-HCC=46.6±37.5	16.63	7.71, 25.55	0.000	87.1
Serum ALB level (g/dl)	HBV-HCC vs. HCV-HCC	12 [8, 9, 16, 19, 20, 23, 25, 27, 30, 32, 33, 36]	3572	HBV-HCC=4.0±0.5 HCV-HCC=3.7±0.4	0.25	0.17, 0.37	0.000	84.8
	NBNC-HCC vs. HBV-HCC	9 [8, 9, 16, 19, 20, 25, 30, 32, 33]	1564	NBNC-HCC=4.0±0.5 NBNC-HCC=4.0±0.5	-0.04	-0.09, 0.01	0.156	13.1
	NBNC-HCC vs. HCV-HCC	9 [8, 9, 16, 19, 20, 25, 30, 32, 33]	3253	HCV-HCC=3.7±0.4 NBNC-HCC=4.0±0.5	-0.25	-0.36, -0.13	0.000	87.9
ICG R15 (%)	HBV-HCC vs. HCV-HCC	8 [9, 19, 20, 23, 30, 32, 33, 36]	2700	HBV-HCC=15.0±10.6 HCV-HCC=19.9±11.5	-5.25	-6.21, -4.29	0.000	32.0
	NBNC-HCC vs. HBV-HCC	6 [9, 19, 20, 30, 32, 33]	1008	HBV-HCC=15.2±10.8 NBNC-HCC=15.4±10.2	-0.26	-1.49, 0.97	0.680	0
	NBNC-HCC vs. HCV-HCC	6 [9, 19, 20, 30, 32, 33]	2546	HCV-HCC=19.9±11.5 NBNC-HCC=15.4±10.2	4.56	3.03, 6.10	0.000	52.7
Serum T-Bil level (mg/dl)	HBV-HCC vs. HCV-HCC	12 [8, 9, 16, 17, 19, 20, 23, 25, 27, 30, 33, 36]	3485	HBV-HCC=0.9±0.6 HCV-HCC=0.9±0.6	-0.03	-0.12, 0.05	0.413	76.3
	NBNC-HCC vs. HBV-HCC	8 [8, 9, 16, 19, 20, 25, 30, 33]	1517	HBV-HCC=0.9±0.4 NBNC-HCC=0.8±0.4	0.11	0.004, 0.22	0.042	83.9
	NBNC-HCC vs. HCV-HCC	8 [8, 9, 16, 19, 20, 25, 30, 33]	3082	HCV-HCC=0.9±0.6 NBNC-HCC=0.8±0.4	0.11	0.01, 0.21	0.035	87.5
Platelet count (×10^3/mm)	HBV-HCC vs. HCV-HCC	12 [8, 9, 16, 17, 19, 20, 23, 25, 27, 30, 33, 36]	3485	HBV-HCC=174.9±114.2 HCV-HCC=140.6±200.1	27.57	13.87, 41.27	0.000	72.0
	NBNC-HCC vs. HBV-HCC	8 [8, 9, 16, 19, 20, 25, 30, 33]	1517	HBV-HCC=173.5±116.0 NBNC-HCC=181.5±122.4	-19.79	-35.07, -4.51	0.011	63.7
	NBNC-HCC vs. HCV-HCC	8 [8, 9, 16, 19, 20, 25, 30, 33]	3082	HCV-HCC=141.2±206.9 NBNC-HCC=181.5±122.4	-40.91	-48.65, -33.17	0.000	15.1
Child's grade A	HBV-HCC vs. HCV-HCC	13 [8, 14, 17, 19-22, 24, 26, 28, 33, 34, 37]	13981	HBV-HCC=87.7% HCV-HCC=84.3%	1.04	1.01, 1.07	0.007	62.9
	NBNC-HCC vs. HBV-HCC	9 [8, 14, 20, 24, 26, 33-35, 37]	6736	HBV-HCC=87.8% NBNC-HCC=89.9%	0.97	0.91, 1.03	0.307	85.9
	NBNC-HCC vs. HCV-HCC	8 [8, 14, 20, 24, 26, 33, 34, 37]	11830	HCV-HCC=85.2% NBNC-HCC=89.8%	0.94	0.93, 0.96	0.000	26.7
Tumor size (cm)	HBV-HCC vs. HCV-HCC	14 [8, 9, 16, 17, 19, 20, 22, 23, 25, 27, 30, 32, 33, 36]	3918	HBV-HCC=4.4±3.4 HCV-HCC=3.4±2.2	0.78	0.44, 1.12	0.000	72.0
	NBNC-HCC vs. HBV-HCC	9 [8, 9, 16, 19, 20, 25, 30, 32, 33]	1564	HBV-HCC=3.8±2.9 NBNC-HCC=4.8±3.6	-0.59	-1.01, -0.17	0.006	65.4
	NBNC-HCC vs. HCV-HCC	9 [8, 9, 16, 19, 20, 25, 30, 32, 33]	3253	HCV-HCC=3.3±2.1 NBNC-HCC=4.8±3.6	-1.37	-1.91, -0.83	0.000	87.0
Serum AFP level	HBV-HCC vs. HCV-HCC	10 [9, 16, 19, 20, 24, 25, 27, 30, 33, 36]	3224	HBV-HCC=8932.6±6456.4 HCV-HCC=1145.6±7081.8	2676.32	-112.27, 5464.90	0.079	92.7
	NBNC-HCC vs. HBV-HCC	8 [9, 16, 19, 20, 24, 25, 30, 33]	1317	HBV-HCC=9122.0±6651.6.2 NBNC-HCC=4349.1±3689.9	2051.21	-5.26, 4107.68	0.051	88.7
	NBNC-HCC vs. HCV-HCC	8 [9, 16, 19, 20, 24, 25, 30, 33]	3106	HCV-HCC=1088.5±6849.7 NBNC-HCC=4584.5±3914.4.8	-650.49	-1.50, 221.25	0.144	49.9
Capsule formation	HBV-HCC vs. HCV-HCC	10 [8, 15-17, 23, 25, 31, 32, 34, 36]	2139	HBV-HCC=52.8% HCV-HCC=64.5%	0.97	0.86, 1.09	0.587	51.9
	NBNC-HCC vs. HBV-HCC	8 [8, 15, 16, 25, 31, 32, 34, 35]	1566	HBV-HCC=61.1% NBNC-HCC=61.4%	1.04	0.89, 1.21	0.616	61.8
	NBNC-HCC vs. HCV-HCC	7 [8, 15, 16, 25, 31, 32, 34]	1699	HCV-HCC=64.1% NBNC-HCC=58.6%	1.10	0.99, 1.22	0.074	18.4
Intrahepatic metastases/ satellite nodules	HBV-HCC vs. HCV-HCC	9 [9, 14-16, 24, 28, 31, 36]	1112	HBV-HCC=22.3% HCV-HCC=16.7%	1.40	1.10, 1.78	0.007	60.9
	NBNC-HCC vs. HBV-HCC	7 [9, 14-16, 24, 31, 34]	5625	HBV-HCC=21.8% NBNC-HCC=27.3%	1.18	0.73, 1.90	0.507	75.6
	NBNC-HCC vs. HCV-HCC	7 [9, 14-16, 24, 31, 34]	11050	HCV-HCC=16.3% NBNC-HCC=27.3%	0.71	0.54, 0.95	0.022	43.6
Vascular invasion	HBV-HCC vs. HCV-HCC	10 [8, 17, 21-24, 26-28, 32]	2613	HBV-HCC=22.9% HCV-HCC=21.2%	1.27	0.85, 1.88	0.242	78.6
	NBNC-HCC vs. HBV-HCC	4 [8, 24, 26, 32]	746	HBV-HCC=15.7% NBNC-HCC=9.2%	1.62	0.93, 2.83	0.090	17.4
	NBNC-HCC vs. HCV-HCC	4 [8, 24, 26, 32]	658	HCV-HCC=12.12% NBNC-HCC=9.17%	1.12	0.43, 2.89	0.813	60.0
Coexisting cirrhosis	HBV-HCC vs. HCV-HCC	17 [8, 9, 14, 15, 17, 20-22, 24-26, 28, 29, 31-34]	14290	HBV-HCC=48.0% HCV-HCC=49.7%	0.90	0.83, 0.98	0.011	64.9
	NBNC-HCC vs. HBV-HCC	13 [8, 9, 14, 15, 20, 24-26, 29, 31-34]	6842	HBV-HCC=49.1% NBNC-HCC=27.9%	1.53	1.30, 1.80	0.000	68.0
	NBNC-HCC vs. HCV-HCC	13 [8, 9, 14, 15, 20, 24-26, 29, 31-34]	12962	HCV-HCC=48.9% NBNC-HCC=27.9%	1.65	1.47, 1.84	0.000	45.3

RR: risk ratio; WMD: weighted mean difference; CI: confidence interval; HBV-HCC: hepatitis B virus related hepatocellular carcinoma; HCV-HCC: hepatitis C virus related hepatocellular carcinoma; NBNC-HCC: non-HBV non-HCV hepatocellular carcinoma.

Response to Associate Editor's Comments:

We sincerely thank the associate editor for the constructive comments, which have greatly

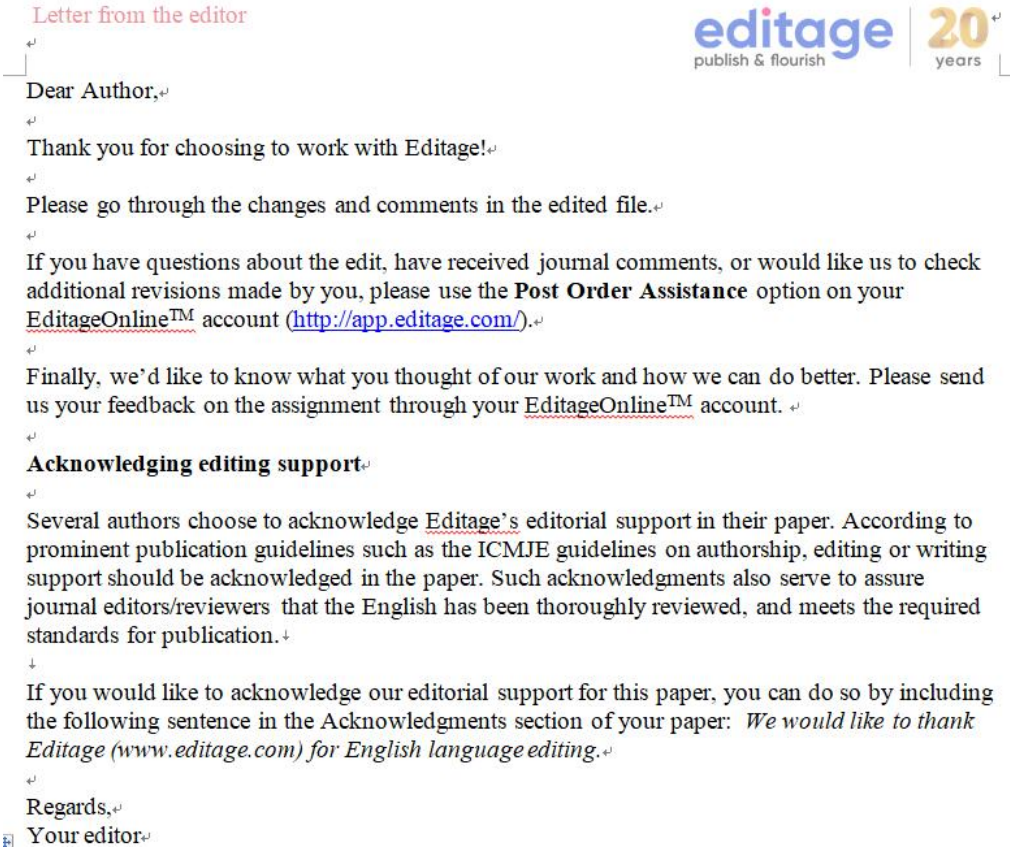
optimized our manuscript. Our manuscript and the supplementary materials have been carefully revised according to the associate editor's instructions. In the following, we respond to the comments one by one, with every comment listed first and the corresponding response following.

Comment 1.

The English writing and academic presentation of manuscript should be improved with the help of a colleague who is expert in academic writing or using the commercial services.

Response 1.

Thank you for the kind reminder. We ask Editage to edit our manuscripts.



Letter from the editor

editage publish & flourish 20 years

Dear Author,

Thank you for choosing to work with Editage!

Please go through the changes and comments in the edited file.

If you have questions about the edit, have received journal comments, or would like us to check additional revisions made by you, please use the **Post Order Assistance** option on your EditageOnline™ account (http://app.editage.com/).

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Acknowledging editing support

Several authors choose to acknowledge Editage's editorial support in their paper. According to prominent publication guidelines such as the ICMJE guidelines on authorship, editing or writing support should be acknowledged in the paper. Such acknowledgments also serve to assure journal editors/reviewers that the English has been thoroughly reviewed, and meets the required standards for publication.

If you would like to acknowledge our editorial support for this paper, you can do so by including the following sentence in the Acknowledgments section of your paper: *We would like to thank Editage (www.editage.com) for English language editing.*

Regards,

Your editor

Comment 2.

I guess, the studies have been selected initially based on availability of survival analysis. Pooling data of characteristics was performed in the above-mentioned studies. Since there is a bias on initial selection of studies and missing HCC studies without evaluation of survival, it cannot be a meta-analysis of HCC characteristics by the HCC underlying disease. I recommend authors to take These into the manuscript.

Response 2.

Thank you for your constructive suggestions, which we have taken into the manuscript.

Comment 3.

In Exclusion criteria, "those with small sample size or large amount of censored data." What is the definition of small sample size and large amount of censored data in this study?

Response 3.

Thank you for pointing out the problems of our manuscript. The small sample size was defined as less than 30 patients, and large amount of censored data meant that the loss of follow-up rate was

greater than 10%. We have made relevant improvements in part 2.3 of the manuscript. The modified part has been marked yellow.

Comment 4.

The presentation of P-values should be uniform. Currently, there is no uniform rule for the presentation of P-values such as P=0.000, P<0.05 and P<0.01

Response 4.

We would like to sincerely thank the associate editor for carefully assessing our manuscript and raising the constructive comment. According to your suggestion, we have unified the presentation of *P*-values (*P*<0.05) in part 3.2 of the manuscript. In the '3.3 survival' and '3.5 Subgroup analysis according to hepatitis virus status' sections, the specific values of *P*-values were retained. Because after repeated discussion, all members of our research team believed that the specific values could more accurately reflect the difference of survival rate of HCC in different hepatitis states.

Comment 5.

The term "risk factor" is vague in title of Table 2. I suggest the term "characteristics" as used by the authors as well.

Response 5.

Thank you for the constructive suggestion, which was well taken. We have revised Table 2 according to your suggestion.

Comment 6.

I have major concern with pooling the characteristics as it is currently done by the authors. How did the authors select the studies for inclusion in pooling for characteristics? HR is an index of survival. How can it be used for comparison of characteristics? How the pooling was performed for the characteristics data?

Response 6.

Thank you for pointing out the problems of our manuscript. In this review, HR was only applied to survival analysis, while dichotomous variables were analyzed with RR with a 95% CI, and continuous variables were analyzed using weighted mean difference (WMD) of 95% CI, as shown in Table 2.

Comment 7.

I have major concern with presentation of HR results for survival data. HR is obtained from calculation of mortality or recurrence in a group comparing another group. knowing which group is the reference is important in presentation of figures, tables and result body. For example, "the 5-year overall survival rates were lower in HBV-HCC (HR:0.86, 95% CI: 0.78 to 0.95, P=0.002) and HCV-HCC group (HR:0.87, 95% CI: 0.80 to 0.94, P=0.000) than that in NBNC-HCC group." The reference group based on the sentence structure and Figure 2 is NBNC-HCC group. The HR less than 1 is in favor of higher survival. Here the HRs are less than 1 and it has been stated that the survival is lower in HCV and HBV groups than NBNC group. This issue should be deeply considered in writing and presentation of results.

Response 7.

Thank you very much for your professional suggestions. According to your suggestion, we define the reference group uniformly. When compared with HBV-HCC or HCV-HCC groups, NBNC-HCC was used as the reference group. When comparing different virus-related HCC groups, HBV-HCC was used as the reference group. We have revised the relevant contents in the manuscript, tables and figures. Your suggestions make this review clearer and standardized.

Comment 8.

Where are the "Sensitivity analysis" results?

Response8.

Thank you for pointing out the problems with our manuscript. Based on your kind comments, we have revised and added to the issues mentioned, and added these key information in Figure 3.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 1 Jun 2022

Authors have done a good job revising the manuscript. This version is much improved and my comments have been fully addressed. However, there are some major methodological concerns raised by the AE and Reviewer 1 that should be evaluated thoroughly.

REFEREE: Reviewer | **Revision** (1) 8 Jun 2022

Authors were respond to all comments, but I think that it is better the heteraogenity rate in all body of manuscript mentioned as real percent. (For example the $I2 \geq 50\%$ and $P \leq 0.10$ changed to $I2 = 75\%$ and $P = 0.09$)

REFEREE: Associate Editor | **Revision** (1) 9 Jun 2022

Dear EIC,

Addressed most of the comments and concerns., however, one of the reviewers had an additional correction and also, I have concern remained yet to be followed carefully.

1. Regarding my comment 2, I did not find any changes or corrections in the revised manuscript.

2. In Table 2, the variable gender should be defined as "male gender" or "female gender".

3. I am not convinced with the corrections regarding my major concern as included in my comment 7. The reference group should be clearly included in all tables and manuscript body and the included HR should be harmonized accordingly. I can add few examples:
a. Lines 161-165, while 5-year RFS is higher in NBNC-HCC than HBV- and HCV-HCC, HR is higher than 1. Here, HBNC is compared with HBV and HCV (both here looks like reference to me here) and HR higher than 1 means lower survival of HBNC than HCV and HBV.
b. In Tables 3-5, the reference groups are not defined yet.
c. In Figure 2, the reference groups are not defined yet.
d. Line 180 and 183, I suggest "HBV-HCC vs. NBNC-HCC" instead of "NBNC-HCC vs. HBV-HCC".
e. Line 181 and 184, I suggest "HCV-HCC vs. NBNC-HCC" instead of "NBNC-HCC vs. HCV-HCC".

4. I suggest to add Figures 3 and 4 as supplementary figures.

Regards

Seyed Moayed Alavian: EIC | **Revision** (**1**) 9 Jun 2022

Dear Authors,

Please follow the peer-review comments and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear editors and reviewers,

Thank you very much for your positive attitude towards our manuscript titled “Comparison of clinical characteristics and postoperative prognosis among HBV-related, HCV-related and non-HBV non-HCV hepatocellular carcinomas: A systematic review and meta-analysis." These comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researchers. We have studied all the comments carefully, revised them all and answered all the questions of the reviewers and associate editor, hoping to get approval. The corrections in the manuscript and supplementary materials are highlighted in yellow, and the responds to the comments are as follows.

Reviewer 1

Authors have done a good job revising the manuscript. This version is much improved and my comments have been fully addressed. However, there are some major methodological concerns raised by the AE and Reviewer 1 that should be evaluated thoroughly.

Response: Thank you very much for your professional suggestion. We have carefully and deeply revised all concerns including methodology raised by the AE and another reviewer. According to the suggestions of AE, the bias in the meta-analysis of HCC characteristics caused by the initial selection of studies with survival data was comprehensively and deeply explained and modified. Meanwhile, clear reference groups and corresponding HR were defined and selected in all manuscripts, tables and figures. In addition, the heterogeneity in the manuscript proposed by another reviewer was revised to the actual percentage. These comments are of great value to the revision and perfection of our paper.

Reviewer 2

Authors were respond to all comments, but I think that it is better the heteraogenity rate in all body of manuscript mentioned as real percent. (For example the $I^2 \geq 50\%$ and $P \leq 0.10$ changed to $I^2 = 75\%$ and $P = 0.09$)

Response: Thank you so much for your constructive suggestions. This suggestion was well taken. We have revised the heterogeneity in full manuscript to the actual percentage. The modified parts have been highlighted in yellow. Some significant revisions are listed below for your convenience.

HCV-HCC groups (HR: 1.14, 95% CI: 1.06 to 1.23, P=0.001) than in the NBNC-HCC group. The above results showed high heterogeneity (HCV-HCC vs. HBV-HCC, I^2: 48.7%, P=0.004; HBV-HCC vs. NBNC-HCC, I^2: 66.5%, P=0.000; HCV-HCC vs. NBNC-HCC, I^2: 63.7%, P=0.000; Figure 2a, c, and e).

group was lower than that in the HBV-HCC group (HR: 1.38, 95% CI: 1.19 to 1.59, P=0.000). All the above results showed high heterogeneity (HCV-HCC vs. HBV-HCC, I^2: 73.1%, P=0.000; HBV-HCC vs. NBNC-HCC, I^2: 58.7%, P=0.002; HCV-HCC vs. NBNC-HCC, I^2: 72.1%, P=0.000; Figure 2b, d, and f).

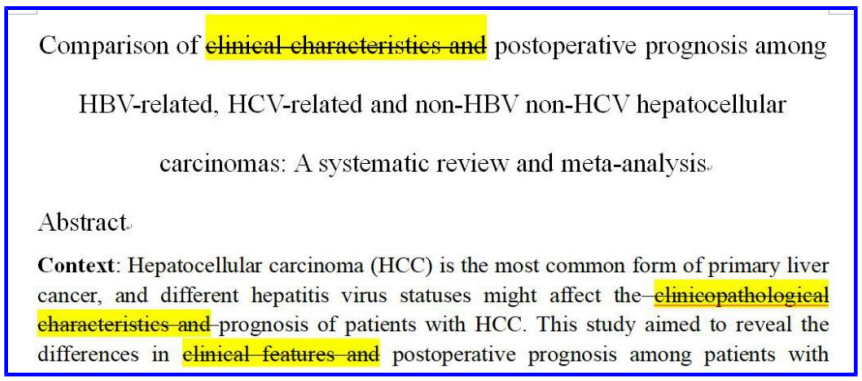
Associate Editor

(1) Regarding my comment 2, I did not find any changes or corrections in the revised manuscript.

Response (1): We are very sorry that this comment has not been well resolved in last response. We planned to explain this bias in limitation section. However, we made a stupid mistake of uploading a second-to-last revised version, making it impossible for you to review this modification. We apologize again and thank you very much for giving us a chance to modify it. As you mentioned before, this study focused on the prognostic differences of postoperative HCC patients with various virus states. All included subjects were postoperative HCC patients with survival data, which caused a certain degree of bias in the results of HCC characteristics. After considerable discussion with the research members and statistical experts, we have systematically and comprehensively revised the full manuscript as follows.

Firstly, we have removed the relevant contents of clinical characteristics in the title,

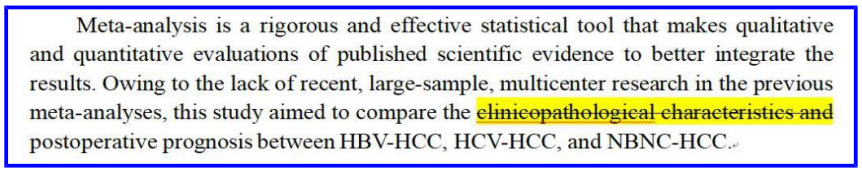
Abstract, and Context, so as to concentrate the prognosis as research emphasis.



Comparison of ~~clinical characteristics and~~ postoperative prognosis among HBV-related, HCV-related and non-HBV non-HCV hepatocellular carcinomas: A systematic review and meta-analysis.

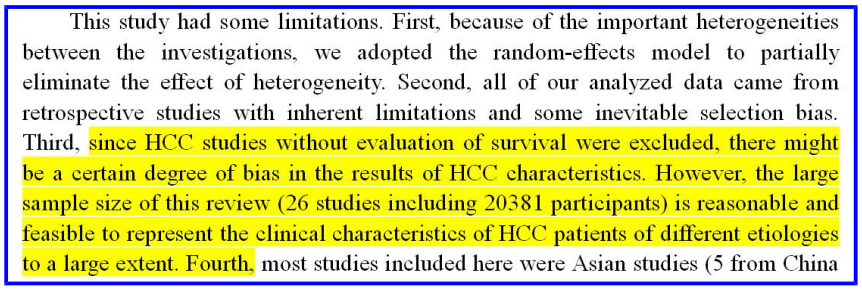
Abstract

Context: Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, and different hepatitis virus statuses might affect the ~~clinicopathological characteristics and~~ prognosis of patients with HCC. This study aimed to reveal the differences in ~~clinical features and~~ postoperative prognosis among patients with



Meta-analysis is a rigorous and effective statistical tool that makes qualitative and quantitative evaluations of published scientific evidence to better integrate the results. Owing to the lack of recent, large-sample, multicenter research in the previous meta-analyses, this study aimed to compare the ~~clinicopathological characteristics and~~ postoperative prognosis between HBV-HCC, HCV-HCC, and NBNC-HCC.

Secondly, although there is a certain bias in initial selection of studies, the large sample size (26 studies including 20381 participants) is reasonable and feasible to represent the clinical characteristics of HCC patients of different etiologies to a large extent. These results are authentic and have a great value for the follow-up research. Therefore, we maintained the relevant contents about clinical characteristics in Results part, and emphasized the limitations of this study in Conclusions section.



This study had some limitations. First, because of the important heterogeneities between the investigations, we adopted the random-effects model to partially eliminate the effect of heterogeneity. Second, all of our analyzed data came from retrospective studies with inherent limitations and some inevitable selection bias. Third, since HCC studies without evaluation of survival were excluded, there might be a certain degree of bias in the results of HCC characteristics. However, the large sample size of this review (26 studies including 20381 participants) is reasonable and feasible to represent the clinical characteristics of HCC patients of different etiologies to a large extent. Fourth, most studies included here were Asian studies (5 from China

Thirdly, we also provided similar authoritative meta-analyses literatures to justify the rationality of this method, as listed below. The first article is the tenth one cited in the manuscript, which analyzed the difference of prognosis and clinical characteristics in

postoperative HCC patients with different viral status. The second one explored the prognosis and clinical significance of Aspartate Aminotransferase-to-Lymphocyte Ratio Index in HCC patients. Similar to our inclusion criteria, these reviews only included studies with survival data.

① Zhou Y, Si X, Wu L, Su X, Li B, Zhang Z. Influence of viral hepatitis status on prognosis in patients undergoing hepatic resection for hepatocellular carcinoma: a meta-analysis of observational studies. World J Surg Oncol. 2011 Sep 21;9:108.

② Peng X, Huang Y, Zhang M, Chen Y, Zhang L, He A, Luo R. Prognostic and Clinical Significance of Aspartate Aminotransferase-to-Lymphocyte Ratio Index in Individuals with Liver Cancer: A Meta-Analysis. Dis Markers. 2022 Feb 9;2022:3533714.

(2) In Table 2, the variable gender should be defined as "male gender" or "female gender".

Response (2): We thank AE for this kind reminder. We have made corresponding improvement of replacing "gender" by "male gender" in Table 2.

Table 2 Meta-analysis of characteristics for HCC patients with different hepatitis virus status.

Characteristic	Group	Number of studies	Number of patients	Results
Age (years)	HCV-HCC vs. HBV-HCC	14 [8, 9, 15-17, 19-21, 24, 25, 30, 32, 33, 36]	4714	HBV-HCC=55.8±11.7 HCV-HCC=67.3±7.9
	HBV-HCC vs. NBNC-HCC	11 [8, 9, 15, 16, 19, 20, 24, 25, 30, 32, 33]	1777	HBV-HCC=55.8±10.4 NBNC-HCC=68.2±9.3
	HCV-HCC vs. NBNC-HCC	11 [8, 9, 15, 16, 19, 20, 24, 25, 30, 32, 33]	3575	HCV-HCC=67.6±7.8 NBNC-HCC=68.0±9.6
Male gender	HCV-HCC vs. HBV-HCC	22 [8, 9, 14-17, 20-28, 30-34, 36, 37]	15839	HBV-HCC=81.6% HCV-HCC=73.4%
	HBV-HCC vs. NBNC-HCC	16 [8, 9, 14-16, 20, 24-26, 30-35, 37]	7909	HBV-HCC=82.6% NBNC-HCC=81.8%
	HCV-HCC vs. NBNC-HCC	15 [8, 9, 14-16, 20, 24-26, 30-34, 37]	14238	HCV-HCC=73.5% NBNC-HCC=81.8%

(3) I am not convinced with the corrections regarding my major concern as included in my comment 7. The reference group should be clearly included in all tables and manuscript body and the included HR should be harmonized accordingly. I can add few examples.

Response (3): We would like to sincerely thank the AE for carefully assessing our investigation and raising the constructive comment, which greatly optimizes its quality. Defining and choosing a clear reference group and corresponding HR could objectively emphasize the research results. We have introduced a reference group in both the manuscript and supplementary materials. When compared with HBV-HCC or HCV-HCC groups, NBNC-HCC was used as the reference group. Similarly, HBV-HCC was defined as the reference group when compared with HCV-HCC. We have

revised the relevant contents in the manuscript, tables and figures. The modified parts have been marked yellow.

a. Lines 161-165, while 5-year RFS is higher in NBNC-HCC than HBV- and HCV-HCC, HR is higher than 1. Here, HBNC is compared with HBV and HCV (both here looks like reference to me here) and HR higher than 1 means lower survival of HBNC than HCV and HBV.

In lines 161-165, NBNC-HCC was the control group as described above. HR higher than 1 means that the 5-year RFS of HBV-HCC or HCV-HCC patients were lower than that of NBNC-HCC patients. The modified details are as follows.

3.3.2. 5-year recurrence-free survival

A total of 23 studies reported 5-year RFS, including 22 with HBV-HCC and HCV-HCC, 16 with HBV-HCC and NBNC-HCC, and 15 with HCV-HCC and NBNC-HCC. There were significant differences in 5-year RFS among patients with different hepatitis virus statuses. Compared with patients with NBNC-HCC, patients with HBV-HCC or HCV-HCC had lower 5-year RFS (HBV-HCC vs. NBNC-HCC, HR: 1.33, 95% CI: 1.16 to 1.52, P=0.000; HCV-HCC vs. NBNC-HCC, HR: 1.71, 95% CI: 1.46 to 2.00, P=0.000, respectively). In addition, the 5-year RFS in the HCV-HCC group was lower than that in the HBV-HCC group (HR: 1.38, 95% CI: 1.19 to 1.59, P=0.000). All the above results showed high heterogeneity (HCV-HCC vs. HBV-HCC, I^2: 73.1%, P=0.000; HBV-HCC vs. NBNC-HCC, I^2: 58.7%, P=0.002; HCV-HCC vs. NBNC-HCC, I^2: 72.1%, P=0.000; Figure 2b, d, and f).

b. In Tables 3-5, the reference groups are not defined yet.

According to your professional reminder, we have clearly defined the reference group in Tables 3-5.

Table 3 Subgroup analysis of HCV-HCC and HBV-HCC

Characteristic	Subgroup	5-year OS (HCV-HCC vs. HBV-HCC)					5-year RFS (HCV-HCC vs. HBV-HCC)				
		HR [95%CI]	P^*	P_i	Heterogeneity I^2	Heterogeneity P_i	HR [95% CI]	P^*	P_i	Heterogeneity I^2	Heterogeneity P_i

Table 4 Subgroup analysis of HBV-HCC and NBNC-HCC

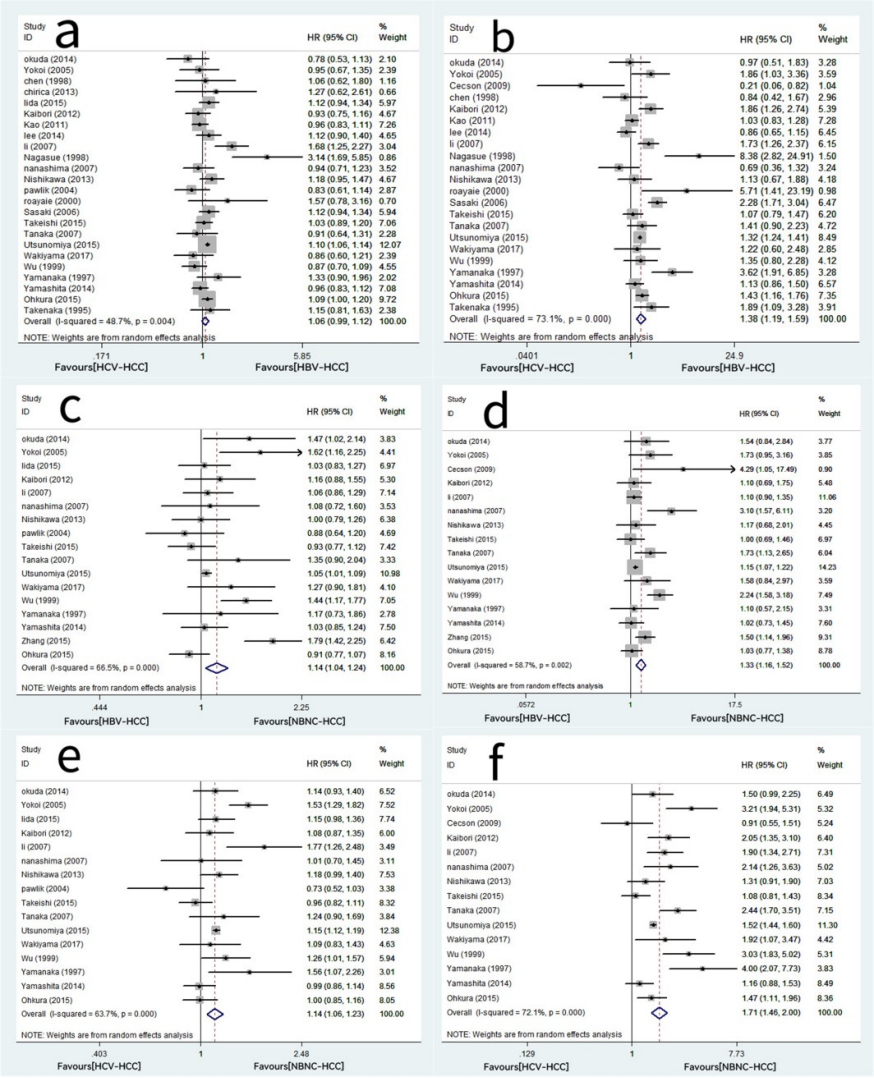
Characteristic	Subgroup	5-year OS (HBV-HCC vs. NBNC-HCC)					5-year RFS (HBV-HCC vs. NBNC-HCC)				
		HR [95% CI]	P^*	P_i	Heterogeneity I^2	Heterogeneity P_i	HR [95% CI]	P^*	P_i	Heterogeneity I^2	Heterogeneity P_i

Table 5 Subgroup analysis of HCV-HCC and NBNC-HCC

Characteristic	Subgroup	5-year OS (HCV-HCC vs. NBNC-HCC)					5-year RFS (HCV-HCC vs. NBNC-HCC)				
		HR [95% CI]	P^*	P_i	Heterogeneity I^2	Heterogeneity P_i	HR [95% CI]	P^*	P_i	Heterogeneity I^2	Heterogeneity P_i

c. In Figure 2, the reference groups are not defined yet.

Thank you for pointing out this issue in the manuscript. We have defined the reference groups, and added the important information in Figure 2.



d. Line 180 and 183, I suggest "HBV-HCC vs. NBNC-HCC" instead of "NBNC-HCC vs. HBV-HCC".

Thank you for your advice. We have modified this expression accordingly.

e. Line 181 and 184, I suggest "HCV-HCC vs. NBNC-HCC" instead of "NBNC-HCC vs. HCV-HCC".

Thanks again for this important advice. We have modified this accordingly.

(4) I suggest to add Figures 3 and 4 as supplementary figures.

Response (4): We thank AE for this professional reminder. We adjusted Figure 3 and 4 as Figure S1 and S2 respectively. We have also made modifications to the corresponding figure captions and manuscript.

3.4. Sensitivity analysis

The random deletion of the literature in this study had little impact on the results, which means that our results were fairly robust (Figure S1).

by significant publication bias, whereas little publication bias was detected for the other groups (Table 6). To remove the influence of publication bias on the combined results, the trim-and-fill analysis was used to handle this bias. Finally, the trim-and-fill method adjusted results were consistent with the original analysis, showing that the combined effect was trustworthy (Figure S2).

Thanks again for your professional and positive suggestions on our manuscript. Please feel free to contact us if you have further questions.

Sincerely,

Zhanjun Guo & Yue Zhao

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (2) 23 Jun 2022

Dear EIC,

Authors addressed all the comments correctly. I have no more comments.

Regards,
AE

Seyed Moayed Alavian: EIC | **Revision** (2) 23 Jun 2022

Dear Authors,

I am delighted to inform that your manuscript is accepted for publication.

Thanks
EIC